REMARKS

Reconsideration and allowance of the present application is respectfully requested in view of the foregoing amendments and the following additional remarks which have addressed all the issues raised in the July 12, 2006, Office Action or otherwise have rendered them moot.

Claims 36 – 39, 41-44 and 67 are now under consideration in this application. Claims 45 – 66 stand withdrawn pursuant to Examiner's imposed restriction requirement. Claim 36 has been amended. The claim amendments are in order to more particularly define and distinctly claim applicant's invention and/or to better recite or describe the features of the present invention as claimed. No new matter is believed to be added.

Claims 36 and 37 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Itay (U.S. 5, 053, 050), in light of Thomas (1997, Taber's Cyclopedic Medical Dictionary, 18th Ed.), and Boden (1999, Clin. Orthop. 376:S84-S94).

Claims 36 – 39, 41 – 44, and 67 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Jakob et al. (1999 WO 99/21497).

Claims 36 –39 and 41 also stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Mears (1985, U.S. Patent 4,553, 272), Vacanti et al. (US 5,736,372), and Caplan et al. (U.S. 4,609,551).

Claims 36 – 38, 41, 42, 44, and 67 stand rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Itay (U.S. 5, 053, 050), Thomas and Boden as applied to claims 36, 37, 40 and 41 above, and further in view of Johnson et al., (U.S. 4,156,296).

Claims 39 and 43 remain rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Itay (U.S. 5, 053, 050), Thomas and Boden as applied to claims 36-38 and 41, 42, 44 and 67 above, and further in view of Wevers (U.S. 4,246,660) and Dunn et al.

Rejections under 35 U.S.C. § 102(b) - Itay

Claims 36 and 37 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Itay (U.S. 5, 053, 050), in light of Thomas (1997, Taber's Cyclopedic Medical Dictionary, 18th Ed.), and Boden (1999, Clin. Orthop. 376:S84-S94). According to the Examiner, Itay teaches a composition produced *in vitro*, comprising a biocompatible carrier material and chondrocytes

which are implanted into defective bones. Regarding prior arguments proffered by Applicants to distinguish over Itay, the Examiner asserts that the phrase "joint construct" does not convey any definite structural articulation nor does the Applicants' argument that Itay does not teach "in vitro opposite side by side placement on biocompatible materials" patentably distinguish over Itay. Applicants disagree and respectfully traverse as follows.

A claim is anticipated under 35 U.S.C. §102(b) only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *See Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Moreover, elements must be arranged as required by the claim. *See In re Bond*, 910 F.2d 831(Fed. Cir. 1990).

As stated in the instant specification, (page 1, lines 22-27) "U.S. 5,053,050 describes compositions for the repair of cartilage **or** bone, cartilage or bone cells being incorporated into a biological, resorbable carrier substance which contains serum, fibrinogen and thrombin." In particular, U.S. 5,053,050, describes the immobilization of chondrocytes or osteoblasts (column 3, lines 35 – 45) on a viscoelastic biodegradable matrix (column 4, lines 43-44), comprising serum, fibrinogen, thrombin, calcium chloride and aprotonin (column 2, lines 38-42).

Applicants believe that as now amended, independent claim 36 is patentably distinct from any teachings or suggestions by Itay. As clearly stated in the specification of U.S. 5,053,050, it teaches a composition for the repair of cartilage or bone, said composition comprising chondrocytes **or** osteoblasts immobilized on biocompatible viscoelastic media. Although the viscoelastic composition of U.S. 5,053,050 may be poured into any geometric configuration in order to affect a repair of damaged tissue (column 4, lines 65-67), the term "***in vitro*** joint construct" as opposed to previously presented "joint construct" now connotes a definite structural articulation which cannot reasonably be associated with the U.S. 5,053,050 patent. At least under 35 U.S.C. § 102(b), the elements of the '050 patent are not arranged as required by the claims of the present application. *See In re Bond*, 910 F.2d 831(Fed. Cir. 1990).

The Examiner asserts that the phrase "definite structural articulation" does not appear anywhere within the original specification and that indeed, the claims do not recite or reasonably imply a "definite structural articulation" either explicitly or in light of the specification as filed. Applicants believe that the Examiner's failure to appreciate the structural articulation of claim 36

is largely responsible for the maintenance of this ground for rejection and will now address that matter.

As a matter of claim construction, the word "construct" in its plain and ordinary sense, means forming an object by putting together parts of that object. As made explicitly clear in claim 36, that object is a biological joint. The different parts of that object is a joint side and an anchor side articulated in such a way that the sides are opposed to each other. The Examiner is respectfully referred to the Brief Description of the Drawings section on page 15 of the specification and to Figures 1c and 1d particularly to see Applicants articulation of the construct in the form of drawings. Indeed, Figure 1c is explicitly an articulation of a "cartilage-bone" construct of the present invention. In said Figure 1c, a joint side is clearly seen oppositely disposed to an anchor side. In construing the claims in light of the specification, the Examiner is respectfully asked to not ignore the teachings of the drawings as well.

Thus, when Applicants insist that unlike Itay, mere recitation of an "in vitro joint construct" having oppositely disposed components connotes a definite structural articulation that cannot be reasonably associated with Itay, Applicants ask the Examiner to assess that argument in light of the word "connote" which means "to signify in addition to the primary meaning; imply; to involve as a condition." Itay teaches a composition for repairing damaged joint; it does not teach a construct having any defined structures. Applicants believe that "in vitro joint construct" having two sides, placed opposite each other as articulated in the drawings and teaching of this invention in no way approximates or resembles Itay's pouring of osteocytes **or** chondrocytes contained in a viscoelastic media unto a damaged joint to effect ***in vivo*** repair. Clearly, Itay's invention has no defined structure associated with it and for that at least, there is no basis for maintaining this ground for rejection.

On the first paragraph of page 4, the Examiner asserts that the Applicant was not claiming an "in vitro construct", but rather a construct "produced at least partly in vitro." Applicants regret that a key amendment to independent claim 36 as presented in the April 24, 2006, amendment appears not to have been considered by the Examiner inviting Applicants to question the finality of the Office Action to which the instant response is directed. Basically, in order to advance the prosecution of this invention, and further in light of conversations had with the Examiner, Applicants had amended claim 36 to explicitly refer to a biological joint construct "produced in vitro," by deleting the phrase "at least partly." In any case, Applicants believe that

as previously presented, a biological joint construct produced *in vitro* is indeed an *in vitro* joint construct. To make that more explicitly clear and to further distinguish the instant invention from Itay, claim 36 has been amended to distinctly refer to an "*in vitro* joint construct." Applicants assert that Itay's mere pouring of chondrocytes **or** osteocytes immobilized in a viscoelastic media unto a damaged joint does not patentably anticipate an "*in vitro* joint construct" of the present invention and for that at least, there is no basis for maintaining this ground for rejection.

Applicants further hope that the above amendments clarify the distinction between Itay and the instant invention. Particularly, Applicants ask the Examiner to bear in mind that Itay's composition never used chondrocytes and osteocytes conjunctively and never in any structural articulation ***in vitro***. Although, the composition of U.S. 5,053,050 may use chondrocytes or osteoblasts, *in vitro*, either group of cells **must** be used disjunctively. See for example column 3, line 42 referring to a "population expressing a chondrogenic or osteogenic phenotype." The mere disjunctive use of chondrocytes or osteocytes alone patentably distinguishes Itay from the instant invention.

Applicants are concerned by the Examiner's assertion that her rejection "is not made over the starting material of Itay, but over the finished product." Applicants respectfully assert that Itay should be considered for what it teaches and no more. Itay teaches the making of viscoelastic material containing osteocytes **or** chondrocytes that can be used to repair a damaged joint. The finished product of Itay is viscoelastic material containing osteocytes **or** chondrocytes and not, as the Examiner erroneously asserts, a repaired joint. Obviously, the joint construct of the present invention and the viscoelastic material of Itay are all directed to the same end – the healing of damaged joint, but that alone should not form a basis for rejecting the patentability of the product of the instant invention merely because it can be applied to a process whereas the relevant inquiry is whether the product of the instant invention is patentably distinct from the product of the prior art. Where that relevant inquiry is made, Applicants believe that the Examiner will form the same conclusion that both inventions are patentably distinguishable.

The Examiner also asserts that she finds the Applicant's argument about "in vitro opposite side by side placement on biocompatible materials" confusing since according to the Examiner, "the phrase is not defined or even recited in the specification." As amended, the

claims now require the sides to be on opposite faces. Support for that structural articulation may be found on the Figures of the present invention e.g. Figure 1c.

Finally, as amended, claim 36 now incorporates the limitation that the joint side is firmly connected to the anchor side of the in vitro joint construct. Support for that limitation may be found in the last paragraph of page 11 and the first paragraph of page 12 where fibrin adhesion is taught as one method of attachement. Literal phraseology may be found in the description of Figure 1c, needless to mention that this in vitro "firm connectedness" of the joint and anchor side is not taught or suggested by Itay, negating again, the basis for the instant rejection.

In the prior Office Actions, the Examiner recognized that the *in vitro* placement of chondrocytes and/or chondroblasts on one side and osteoblasts and or osteocytes on the other side, is not taught by U.S. 5,503,050, but insists that this limitation is not recited in the claims. Applicants have now explicitly recited this limitation in the claims and it is believed that there is no further basis for maintaining any 35 U.S.C. 102 or 103 rejections over Itay. For that at least, Applicants respectfully ask that this ground for rejection be withdrawn.

Rejections under 35 U.S.C. § 102(b) – Jakob et al.

Claims 36 – 39, 41 – 44, and 67 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Jakob et al. (1999 WO 99/21497).

The Examiner characterized Jakob et al., as teaching a composition comprising bone adhered to cartilage that has been removed from a donor site. The Examiner further asserts that Jakob et al. also teach a composition comprising cartilage cells cultured in vitro on bone-replacement material. By deeming claims 36 –39, 41-44 and 67 as product by process claims, the Examiner asserts that the product of the instant invention is no different from Jakob et al., even if the process may differ. Applicants respectfully disagree with the Examiner and now traverse as follows.

Applicants have made a detailed review of Jakob et al. and have noted particularly, Jakob's teaching that cultured cartilaginous cells come within the ambits of its invention. However, no where did Jakob et al. contemplate, suggest, envisage, teach or render obvious, the making of ***in vitro*** joint construct comprising both **cultured** cartilaginous cells and **cultured**

osseous cells immobilized or anchored in/on **firmly connected** opposite sides of at least one biologically compatible material. The conjunctive use of both cultured cartilaginous cells **and** cultured osseous cells, as now made explicitly clear by way of amendment to claim 36 is patentably distinct from the teachings of Jakob et al.

The Examiner cites the following passages from Jakob et al. as germane to her grounds for rejection:

> The autotransplants, in particular, are mostly columns having an outer cartilage face side and an inner bone face side. Jakob et al. page 2, paragraph 3.
>
> Tissue columns are then removed from a less strained joint site ... the tissue columns that are removed are then inserted into the defect holes. Jakob et al. page 2, paragraph 4.

Applicants do not contend the Examiner's characterization of Jakob et al., but do respectfully contend the assertion that the product of the instant invention, even as product by process claims, are so broad as to encompass bone and a joint in their natural form. Applicants believe that it would be erroneous to now consider claim 36 a product by process claim. Secondly, Applicants believe that all the limitation of claim 36 particularly those limiting it to an *in vitro* joint construct comprising biocompatible material comprising cultured cartilaginous cells and **consisting essentially** of cultured osteoblasts and/or osteocytes and bone substance clearly distinguishes claim 36 from a bone/joint in their natural state.

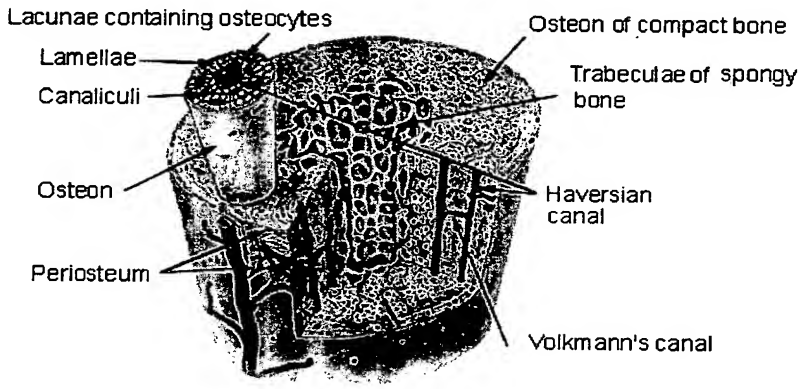
Applicants believe that the mere limitation of claim 36 to use of cultured cells sufficiently distinguishes the i*n vitro* joint construct of the present invention from the natural bone extract of Jakob et al and precludes broadening of the scope of the instant invention to encompass bone in its natural state.

Nor does natural bone tissue have the same structure as tissue engineered bone-substitutes of the present invention. In vivo grown bone tissue is vascularized and contains bone trabeculae and bone marrow with hemopoetic and mesenchymal stem cells, progenitor cells, osteoblasts (bone forming cells), osteoclasts (bone resorbing cells) growth factors, extracellular matrix proteins etc.

Bones in human and other mammal bodies are generally classified into two types 1: Cortical bone, also known as compact bone and 2) Trabecular bone, also known as cancellous or spongy bone. These two types are classified on the basis of porosity and their unit microstructure. Cortical bone is much denser with a porosity ranging between 5% and 10%. Cortical bone is found primary in the shaft of long bones and forms the outer shell around cancellous bone at the end of joints and the vertebrae. The basic first level structure of cortical bone are osteons.

Trabecular bone is much more porous with porosity ranging anywhere from 50% to 90%. It is found in the end of long bones, in vertebrae and in flat bones like the pelvis. Its basic first level structure is the trabeculae.

Compact Bone & Spongy (Cancellous Bone)



As with all biological tissues, cortical bone has a hierarchical structure. This means that cortical bone contains many different structures that exist on many levels of scale. The hierarchical organization of cortical bone is defined in the table below:

Cortical Bone Structural Organization

Level	Cortical Structure	Size Range	h
0	Solid Material	> 3000 mm	—
1	Secondary Osteons [A] Primary Osteons [B] Plexiform (C) Interstitial Bone	100 to 300 mm	< 0.1

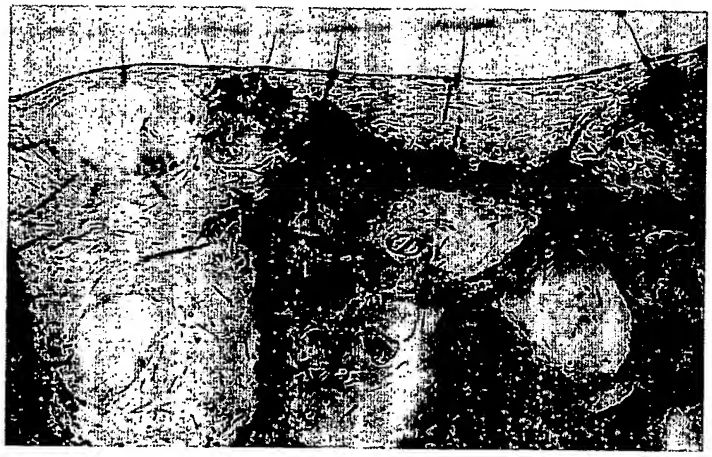
2	Lamellae [A,B*,C*] Lacunae [A,B,C,D] Cement Lines [A]	3 to 20 mm	< 0.1
3	Collagen- Mineral Composite [A,B,C,D]	0.06 to 0.6 mm	<0.1

[A] - denotes structures found in secondary cortical bone
[B] - denotes structures found in primary lamellar cortical bone
[C] - denotes structures found in plexiform bone
[D] - denotes structures found in woven bone
* - indicates that structures are present in b and c, but much less than in a

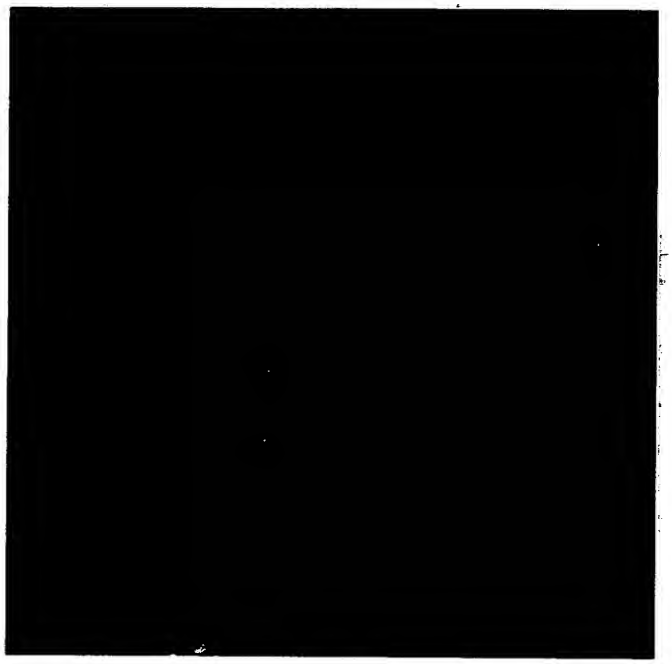
Table 1. Cortical bone structural organization along with approximate physical scales. The parameter h is a ratio between the level and the next most macroscopic level. This parameter is used in RVE analysis.

On the other hand, tissue engineered bone substitutes present an entirely different morphology. Typically, tissue engineered bone substitutes is achieved by *in vitro* composition of biomaterial as carrier matrix and use of cultured bone tissue forming cells. Cell seeding onto the biomaterial is managed by suspending cells in fibrinogen solution to immobilize the cells in the carrier matrix. Cell suspension can be delivered to different biomaterials as carrier matrix.

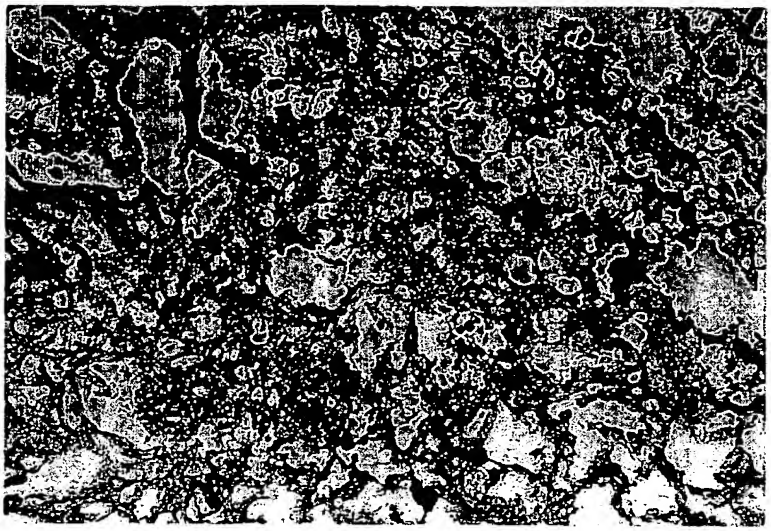
One Example is the use of porous Matrix containing Tricalciumphosphate TCP, 60 5 porosity, Low grade interconnectivity of pores, compression stability, as shown in the following diagram of *in vitro* tissue engineered bone substitute with TCP (dark blue) and cultured osteoblasts in fibrin (light blue) light microscopy 200x.



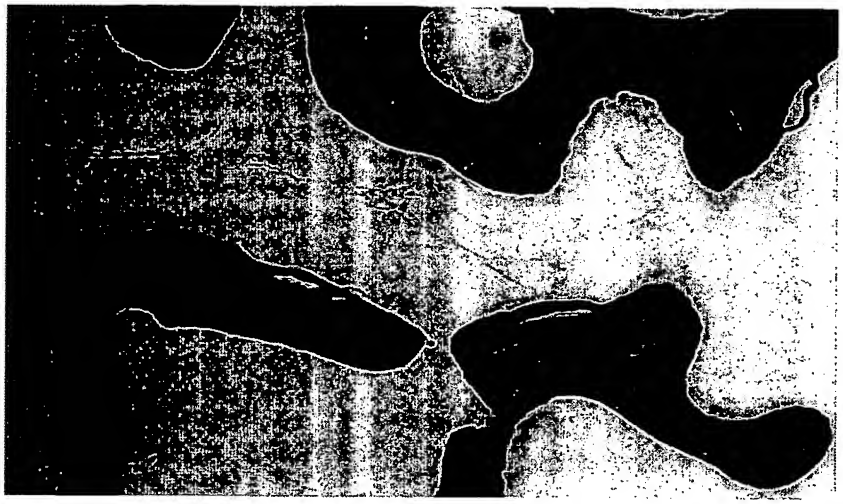
Similarly, the diagram below shows immunfluoresence of TCP construct. Lighter areas indicate bone specific adhesion molecules synthesized by bone forming cells. 200x



In another Example, Applicants present a tissue engineered bone substitute showing composition with hydroxyapatite-Collagen Matrix wherein Collagen Type 1 sponge is impregnated with hydroxyapatite crystals, soft material, porosity ca. 90%, no compression stability. The diagram below shows H.E. staining of HA-Collagen sponge (blue) with bone forming cells (red, only in center) light microscopy 200x .



Also, Applicants show a composition with processed Cancellous Bone Matrix. In the diagram below, a cellular chemically processed or heat sterilized bone matrix composed of hydroxyapatite and collagen type 1 fibrils, porosity 90%, high interconnectivity, Porosity, compression stability, is used. The diagram below shows stain of cancellous bone matrix (red) with bone forming cells (blue) synthesizing bone matrix (blue). 100x



Applicants have presented a somewhat detailed histological profile to show that there are patentably distinct differences between a fully tissue-engineered bone/joint substitute of the present invention and that of Jakob et al., which at best can be characterized as teaching a partial

as opposed to fully tissue-engineered joint substitute. Applicants believe that there is no further basis for maintaining this ground for rejection and it is respectfully requested that it be withdrawn.

Rejections under 35 U.S.C. § 102(b) – Mears, Vacanti et al., and Caplan et al.

Claims 36 – 39 and 41 also stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Mears (1985, U.S. Patent 4,553, 272), Vacanti et al. (US 5,736,372), and Caplan et al. (U.S. 4,609,551).

According to the Examiner, Mears teaches a composition comprising cartilage cells in a biocompatible carrier that is implanted into living bone and colonized by osseous tissue.

From the foregoing, this invention, directed to a fully tissue-engineered bone/joint substitute having a definite structural articulation and which comprises the use of cultured cartilaginous and cultured osseous cells arranged in/on opposite sides of at least one biocompatible material is patentably distinct from the teachings of Mears et al. As such, Applicants ask that this ground for rejection be withdrawn.

According to the Examiner, Vacanti et al. teaches a composition comprising cartilage cells on a biocompatible material that is implanted into living bone and colonized on osseous tissue.

From the foregoing, this invention, directed to a fully tissue-engineered bone/joint substitute having a definite structural articulation and which comprises the use of cultured cartilaginous and cultured osseous cells arranged in/on opposite sides of at least one biocompatible material is patentably distinct from the teachings of Vacanti et al. As such, Applicants ask that this ground for rejection be withdrawn.

According to the Examiner, Caplan et al. teaches a composition comprising fibroblasts and a growth factor in a fibrin clot that is implanted into living bone and gives rise to both bone and cartilage.

Again, from the foregoing, this invention, directed to a fully tissue-engineered bone/joint substitute having a definite structural articulation and which comprises the use of cultured cartilaginous and cultured osseous cells arranged in/on opposite sides of at least one

biocompatible material is patentably distinct from the teachings of Caplan et al. As such, Applicants ask that this ground for rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 36 – 38, 41, 42, 44, and 67 stand rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Itay (U.S. 5, 053, 050), Thomas and Boden as applied to claims 36, 37, 40 and 41 above, and further in view of Johnson et al., (U.S. 4,156,296).

According to the Examiner's assertions in a prior office action, Johnson et al. teaches a joint construct that in anchored into the bone shaft with a cylindrical peg. As motivation for combining Johnson et al. and U.S. 5,053,050, the Examiner argued that a skilled artisan would appreciate that a peg articulated into a bone shaft would produce a more secure fit than would two flat ends touching. Regarding the reasonableness of the expectation of success in combining Johnson et al. and U.S. 5,053,050, the Examiner asserted that U.S. 5,053,050 can be constructed in any shape or size (column 5, lines 3 -6).

Applicants hereby reiterate the arguments made in traversing the 35 U.S.C. § 102(b) above and particularly contend that a proper 103(a) rejection cannot be anchored on U.S. 5,053,050 based on the fact that the teachings of U.S. 5,053,050 differ fundamentally from the inventions of the present application as claimed and the deficiencies are not curable by the Examiner's combination.

In particular, Itay (U.S. 5,053,050) does not teach nor suggest, nor render obvious, nor provide motivation for a fully tissue-engineered bone/joint substitute having a definite structural articulation and which comprises the use of cultured cartilaginous and cultured osseous cells arranged in/on opposite sides of at least one biocompatible material as claimed in amended claim 36. Furthermore, no combination of Itay and Johnson can cure the limitations of either art in terms of meeting the elements of cultured cartilaginous and cultured osseous cells used conjunctively to make a tissue-engineered bone/joint substitute *in vitro*. As such, Applicants respectfully ask that this ground for rejection be withdrawn.

Claims 39 and 43 remain rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Itay (U.S. 5, 053, 050), Thomas and Boden as applied to claims 36-38 and 40-42 above, and further in view of Weavers (U.S. 4,246,660) and Dunn et al.

According to the Examiner neither 5,053,050 nor Johnson et al. teaches joint constructs or replacements with ligaments or joint capsules, said deficiencies being cured by Weavers et al and Dunn et al. Applicants respectively disagree and traverse as follows.

Applicants reiterate the arguments made in traversing the 35 U.S.C. § 102(b) above and particularly contend that a proper 103(a) rejection cannot be anchored on U.S. 5,053,050 based on the fact that the teachings of U.S. 5,053,050 differ fundamentally from the inventions of the present application as claimed and the deficiencies are not curable by the Examiner's combination.

In particular, U.S. 5,053,050 does not teach nor suggest nor render obvious nor provide motivation for a fully tissue-engineered bone/joint substitute having a definite structural articulation and which comprises the use of cultured cartilaginous and cultured osseous cells arranged in/on opposite sides of at least one biocompatible material as claimed in amended claim 36. As such, the prosthetic ligament device of Weavers comprising a plurality of interwoven parallel cord wrap elements cannot be combined with U.S. 5,053,050 to arrive at the present invention comprising entirely biocompatible materials.

Even if the Examiner insists on making the combination, it is again contended that the combined art cannot meet all the elements of the claimed structural articulation of tissue-engineered joint substitute and as such, there is no basis for the rejections under 35 U.S.C. § 103 (a). Applicants respectfully ask that these rejections be withdrawn.

CONCLUSION

All of the stated grounds for rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn and the claims allowed to issue. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

REED SMITH, LLP

Date: _____ By: _____
Toni-Junell Herbert

Date: 8/14/2007 By: _____
Christopher E. Aniedobe
Reg. No. 48, 293

3110 Fairview Park Drive
Suite 1400r
Falls Church, VA 22042
(703) 641-4200

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PATENT TRADEMARK OFFICE